Supporting Information

A Novel Access for Indole-3-substituted Dihydrocoumarins in Artificial Sweetener Saccharin based Functional Ionic Liquid

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General: All the reagents and solvents were purchased from Sigma-Aldrich or Merck chemical Co. and were used directly without any further purification. Organic solvents were concentrated under reduced pressure on a Büchi rotary evaporator. The progress of reaction was checked by thin-layer chromatography. The plates were visualized first with UV illumination followed by iodine. $^1$H NMR spectra were recorded at 200 or 300 MHz using Brucker DRX-200 or 300 spectrometer and are reported in parts per million (ppm) on the $\delta$ scale relative to TMS as an internal standard. Coupling constants ($J$) reported in Hz. $^{13}$C NMR spectra were recorded at 50 or 75 MHz. Mass spectra were obtained using JEOL SX-102 (ESI) instrument. Elemental analysis was performed using a Perkin-Elmer autosystem XL analyzer. All melting points are uncorrected.

Representative experimental procedure for the functional ionic liquid [bmim][Sac]

\[
\begin{align*}
\text{H}_{3}\text{C} & \quad \text{H}_{3}\text{C} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\begin{array}{c}
\text{H}_{3}\text{C} \quad \text{N} \\
\text{N} \\
\text{N} \\
\text{H}
\end{array}\] + \[\begin{array}{c}
\text{C} \quad \text{C} \\
\text{N} \\
\text{N} \\
\text{H}
\end{array}\] \text{Br} \quad \text{Br}

\[\begin{array}{c}
\text{80°C} \\
\text{24h, reflux}
\end{array}\] \quad \text{H}_{3}\text{C} \quad \text{H}_{3}\text{C} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H}

\text{acetone, 30h, rt, stirring}

Figure 1 Representative procedure for synthesis of [bmim][Sac].

Representative experimental procedure for the sodium salt of saccharinate.

A three-neck 100 ml round bottom flask was fitted with overhead stirrer, condenser and inlet/outlet for nitrogen atmosphere. The flask was charged with 7.32g saccharin (0.04 mol) and 2.16g (0.04 mol) anhydrous sodium methoxide in 50 ml anhydrous methanol. The mixture was stirred and heated to reflux for about 10-20 minutes under nitrogen. Most of the solids went into solution. The system was then set-up for distillation. Methanol was removed under reduced pressure. Colorless solids of sodium saccharin (yield 90%) remained in the flask.
Preparation of the 1-n-butyl-3-methylimidazolium saccharinate [bmim][Sac]:

The sodium saccharinate (27.0 g, 0.112 mol) was added into a solution of 1-n-butyl-3-methylimidazolium bromide (BMImBr) (24.6 g, 0.112 mol) in 100 mL acetone at room temperature. After stirring for 24 h, the reaction mixture was filtered through a plug of celite. The volatiles were removed under reduced pressure overnight. Viscous oil was obtained. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta_H\): 0.89 (t, \(J = 7.6\) Hz, 3H), 1.28-1.21 (m, 2H), 1.80-1.73 (m, 2H), 3.86 (s, 3H), 4.17 (t, \(J = 7.1\) Hz, 2H), 7.71–7.78 (m, 4H), 7.75 (s, 1H), 7.82 (s, 1H), 9.18 (s, 1H). \(^1\)C NMR (DMSO-\(d_6\), 50 MHz) \(\delta_c\): 13.20, 18.70, 31.30, 35.71, 48.43, 119.98, 122.20, 122.45, 123.51, 128.25, 130.99, 131.46, 133.00, 136.47, 167.88.

General procedure for the synthesis of indole-3-dihydrocoumarin derivatives via one pot multicomponent reaction of Indole, Salicyldehyde and Meldrum acid:

A mixture of salicylaldehyde or 4-OMe-salicylaldehyde (1 mmol), meldrum acid (1 mmol), indole derivatives (1 mmol) and [bmim]Sac (2 ml) in a 50mL flask, and was vigorous stirred at room temperature (25–29 °C) for 8-10h, the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was extracted with ethyl acetate (3×20 ml). Then the combined organic part was dried over Na\(_2\)SO\(_4\) and the solvent was evaporated to yield a crude residue. The crude products thus obtained were purified by column chromatography (silica gel, 60-120 mesh; ethyl acetate/petroleum ether). All desired products were characterized by \(^1\)H NMR, \(^1\)C NMR and mass spectra.

Reusability of the [C\(_4\)MIM][Sac]: After completion of the reaction, the reaction mixture was diluted with EtOAc (20 mL) followed by addition of a 5 mL of water. The EtOAc layer was separated. The EtOAc extract was dried (Na\(_2\)SO\(_4\)) and concentrated under vacuo to obtain the crude product. The aqueous extract/layer containing the ionic liquid was concentrated under vacuum at 80°C for 60 min to recover the IL which was found to be identical (spectral data) with an authentic sample of [bmim][Sac] (unused ionic liquid). The recovered IL was reused for 4 successive batches of reactions at rt to afford crude product after usual work-up (Table 1).

### Table 1 Reusability of 1-methyl-3-(n-butyl) imidazolium Saccharinate [(C\(_4\)MIM)Sac] ionic liquid in indole -3 dihydacoumarin synthesis

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<td>Yield (%)</td>
<td>93</td>
<td>91</td>
<td>87</td>
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\(^a\)Reaction conditions: Indole (1.0 mmol), meldrum acid (1.0 mmol), salicylaldehyde (1.0 mmol), ionic liquid (2.0 mL), rt, 8 h. \(^b\) Isolated yield.
Characterization data for synthesized compounds:

4-(1H-indol-3-yl)chroman-2-one (a)

Physical state: oily. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.20 (s, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.31-7.18 (m, 1H), 7.13-6.79 (m, 5H) 6.79 (s, 1H), 4.63 (t, $J = 6.18$ Hz, 1H), 3.26 (dd, $J = 7.6$, 15.8 Hz, 1H), 3.09 (dd, $J = 5.6$, 15.8 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 168.6, 151.8, 136.9, 128.7, 128.4, 126.2, 125.9, 124.8, 122.7, 122.5, 120.0, 119.0, 117.2, 115.2, 111.8, 36.5, 32.8. Molecular formula C$_{17}$H$_{13}$NO$_2$. ESI MS (m/z) = 264 (M+H). Analysis calculated for C$_{17}$H$_{13}$NO$_2$: C 77.55, H 4.98, N 5.32. Found: C 77.53, H 4.97, N 5.29.

4-(5-bromo-1H-indol-3-yl)chroman-2-one (b)

Physical state: oily. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.29 (s, 1H), 7.54 (s, 1H), 7.25-7.12 (m, 3H), 7.05-6.95 (m, 3H), 6.67 (d, $J = 2.1$ Hz, 1H), 4.49 (t, $J = 6.1$ Hz, 1H), 3.11 (dd, $J = 6.9$, 15.7 Hz, 1H), 2.97 (dd, $J = 5.6$, 15.7 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 168.4, 151.7, 135.5, 129.0, 128.2, 127.6, 125.7, 125.6, 125.0, 123.7, 121.4, 117.3, 114.9, 113.3, 113.2, 36.5, 32.6. Molecular formula C$_{17}$H$_{12}$BrNO$_2$, ESI MS (m/z): 342 (M+H). Analysis calculated for C$_{17}$H$_{12}$BrNO$_2$: C 59.67, H 3.53, N 4.09. Found: C 59.68, H 3.50, N 4.10.

4-(5-methoxy-1H-indol-3-yl)chroman-2-one (c)

Physical state: White solid, mp: 155-157 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.01 (s, 1H), 7.32-7.21 (m, 2H), 7.15 (t, $J = 5.6$ Hz, 3H), 7.16-7.05 (m, 2H), 6.91 (s, 1H), 4.61 (t, $J = 6.7$ Hz, 1H), 3.81 (s, 3H), 3.23 (dd, $J = 7.6$, 15.7 Hz, 1H), 3.08 (dd, $J = 5.6$, 15.7 Hz, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 168.4, 154.2, 151.7, 131.9, 128.6, 128.2, 126.3, 126.0, 124.7, 123.0, 117.1, 114.7, 112.6, 112.4, 100.9, 36.3, 32.6. Chemical Formula: C$_{18}$H$_{15}$NO$_3$. ESI MS (m/z): 294 (M+H). Analysis calculated for C$_{18}$H$_{15}$NO$_3$: C 73.71, H 5.15, N 4.78. Found: C 73.73, H 5.11, N 4.80.

4-(1-methyl-1H-indol-3-yl)chroman-2-one (d)

Physical state: oily. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.41 (d, $J = 7.9$ Hz, 1H), 7.26-7.15 (m, 3H), 7.10-6.97 (m, 4H), 6.59 (s, 1H), 4.56 (t, $J = 6.1$ Hz, 1H), 3.63 (s, 3H), 3.15 (dd, $J = 7.2$, 15.7 Hz, 1H), 2.98 (dd, $J = 5.6$, 15.7 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 29.7, 32.6, 36.5, 109.7, 113.7, 117.1, 118.9, 119.4, 122.1, 124.6, 126.9, 126.2, 128.2, 128.5, 12.5, 137.5, 151.7, 168.2. Molecular formula: C$_{18}$H$_{15}$NO$_2$. ESI MS (m/z): 278 (M+H). Analysis calculated for C$_{18}$H$_{15}$NO$_2$: C 77.96, H 5.45, N 5.05. Found: C 77.92, H 5.46, N 5.08.

4-(1-allyl-1H-indol-3-yl)chroman-2-one (e)

Physical state: oily. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.52 (d, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.6$ Hz, 3H), 7.29-7.10 (m, 4H), 6.77 (s, 1H), 6.02-5.93 (m, 1H), 5.21 (d, $J = 10.1$ Hz, 1H).
Hz, 1H), 5.09 (d, \(J=17.1\) Hz, 1H), 4.68 (d, \(J=9.9\) Hz, 2H) 4.31 (t, \(J=6.8\) Hz, 1H), 3.27 (dd, \(J=15.7\) Hz, 1H). 13C NMR (50 MHz, CDCl3) \(\delta_c: 168.2, 150.1, 136.9, 135.2, 133.1, 128.5, 128.2, 126.4, 125.8, 124.6, 122.2, 119.5, 119.0, 117.5, 117.1, 114.0, 110.1, 48.8, 36.4, 29.7.


4-(1-allyl-1H-indol-3-yl)-7-methoxychroman-2-one (f)

Physical state: oily. 1H NMR (300 MHz, CDCl3) \(\delta_H: 7.40 (d, J=7.9\) Hz, 1H), 7.26-7.15 (m, 2H), 7.03 (t, \(J=6.41\) Hz, 1H), 6.95 (d, \(J=11.4\) Hz, 1H), 6.65 (s, 1H), 6.62 (d, \(J=2.4\) Hz, 1H), 6.57-6.53 (m, 1H), 5.91-5.80 (m, 1H), 5.21 (d, \(J=9.3\) Hz, 1H), 5.10 (d, \(J=9.3\) Hz, 1H), 4.41 (d, \(J=4.05\) Hz, 2H), 4.23 (t, \(J=6.6\) Hz, 1H), 3.73 (s, 3H), 3.14 (dd, \(J=7.6, 15.7\) Hz, 1H), 2.98 (dd, \(J=5.6, 15.7\) Hz, 1H). 13C NMR (50 MHz, CDCl3) \(\delta_c: 168.4, 160.0, 152.5, 137.1, 133.4, 128.9, 126.0, 122.3, 119.6, 119.2, 118.0, 117.6, 115.5, 114.6, 110.8, 110.3, 102.7, 55.7, 49.0, 36.9, 32.2. Molecular formula: C21H19NO3, ESI MS (m/z): 334 (M+H). Analysis calculated for C21H19NO3: C 75.66, H 5.74, N 4.20. Found: C 75.62, H 5.70, N 4.21.

4-(2-methyl-1H-indol-3-yl)chroman-2-one (g)

Physical state: White solid, mp: 108-110 °C. 1H NMR (300 MHz, CDCl3) \(\delta_H: 7.99 (s, 1H), 7.36 (d, J=7.2\) Hz, 1H), 7.29 (d, \(J=6.74\) Hz, 2H), 7.19-7.07 (m, 2H), 7.04-6.94 (m, 3H), 4.68 (t, \(J=5.9\) Hz, 1H), 3.29 (dd, \(J=13.2, 16.0\) Hz, 1H), 2.99 (dd, \(J=5.2, 16.0\) Hz, 1H), 2.39 (s, 3H). 13C NMR (75 MHz, CDCl3) \(\delta_c: 168.7, 151.9, 135.7, 132.8, 128.5, 128.1, 126.4, 125.6, 124.5, 121.4, 119.5, 119.0, 116.9, 110.7, 108.6, 35.9, 31.9, 12.0. Chemical Formula: C18H15NO2, ESI MS (m/z): 278 (M+H). Analysis calculated for C18H15NO2: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.99; H, 5.41; N, 5.07.

4-(1-ethyl-1H-indol-3-yl)chroman-2-one (h)

Physical state: oily. 1H NMR (300 MHz, CDCl3) \(\delta_H: 7.55 (d, J=7.8\) Hz, 1H), 7.42-7.27 (m, 4H), 7.21-7.10 (m, 3H), 6.81 (s, 1H), 4.66 (t, \(J=6.1\) Hz, 1H), 4.17-4.10 (m, 2H), 3.13 (dd, \(J=5.6, 15.8\) Hz, 1H), 3.29 (dd, \(J=7.5, 15.8\) Hz, 1H), 1.46 (t, \(J=7.3\) Hz, 3H), 2.39 (s, 3H). 13C NMR (75 MHz, CDCl3) \(\delta_c: 168.3, 151.7, 136.6, 128.5, 128.2, 126.4, 126.3, 125.1, 124.6, 122.0, 119.3, 119.1, 117.1, 113.7, 109.9, 41.0, 36.5, 32.7, 15.4. Molecular formula: C19H17NO2. ESI MS (m/z): 292 (M+H). Analysis calculated for C19H17NO2: C 78.33, H 5.88, N 4.81. Found C 78.30, H 5.90, N 4.80.

4-(1-butyl-1H-indol-3-yl)-7-methoxychroman-2-one (i)

Physical state: oily. 1H NMR (300 MHz, CDCl3) \(\delta_H: 7.50 (d, J=7.9\) Hz, 1H), 7.37 (d, \(J=7.2\) Hz, 1H), 7.24 (d, \(J=7.5\) Hz, 1H), 7.14-7.05 (m, 2H), 6.76 (s, 1H), 6.73 (d, \(J=2.4\) Hz, 1H), 6.67-6.63 (m, 1H), 4.61 (t, \(J=8.9\) Hz, 1H), 4.07 (t, \(J=7.1\) Hz, 2H), 3.84 (s, 3H), 3.24 (dd, \(J=7.7, 15.7\) Hz, 1H), 3.08 (dd, \(J=5.6, 15.7\) Hz, 1H), 1.85-1.75 (m, 2H), 1.38-1.30 (m, 2H), .95 (t, \(J=4.4\) Hz,
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.52 (d, $J = 7.9$ Hz, 1H), 7.39-7.24 (m, 2H), 7.18 (d, $J = 4.7$ Hz, 2H), 7.10 (t, $J = 8.9$ Hz, 3H), 6.77 (s, 1H), 4.68 (t, $J = 5.9$ Hz, 1H), 4.07 (t, $J = 7.1$ Hz, 2H), 3.27 (dd, $J = 7.7, 15.7$ Hz, 1H), 3.11 (dd, $J = 5.6, 15.7$ Hz, 1H), 1.85-1.75 (m, 2H), 1.38-1.30 (m, 2H), 94 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 168.3, 151.6, 137.9, 128.5, 128.2, 126.2, 125.8, 124.6, 121.9, 119.2, 119.0, 117.0, 113.4, 109.9, 46.2, 36.5, 32.6, 32.3, 20.2, 13.7. Chemical Formula: C$_{21}$H$_{21}$NO$_2$. ESI MS (m/z):= 320 (M+H). Analysis calculated for C$_{21}$H$_{21}$NO$_2$: C, 78.97; H, 6.63; N, 4.39; Found: C, 78.99; H, 6.62; N, 4.43.

4-(1H-indol-3-yl)-7-methoxychroman-2-one (l)

Physical state: oily: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.08 (s, 1H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 1H), 7.17-7.11 (m, 1H), 7.02 (t, $J = 7.1$ Hz, 1H), 6.94 (d, $J = 11.4$, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 6.61 (d, $j = 2.4$ Hz, 1H), 6.55-6.52 (m, 1H), 4.59 (t, $j = 3.5$ Hz, 1H), 3.72 (s, 3H), 3.41 (dd, $j = 7.6, 15.7$ Hz, 1H), 3.05 (dd, $J = 5.6, 15.7$ Hz, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 166.5, 150.0, 152.5, 137.0, 128.9, 125.9, 122.7, 122.4, 120.0, 119.0, 118.0, 115.7, 111.8, 10.8, 102.7, 55.7, 36.8, 32.2. Molecular formula-C$_{18}$H$_{15}$NO$_3$, ESI MS (m/z):= 294 (M+H). Analysis calculated for C$_{18}$H$_{15}$NO$_3$: C 73.71, H 5.15, N 4.78. Found, C 73.67, H 5.16, N 4.75.
(t, J = 6.1 Hz, 1H), 4.17-4.09 (m, 2H), 3.84 (s, 3H), 3.25 (dd, J = 7.5, 15.7 Hz, 1H), 3.09 (dd, J = 5.64, 15.7 Hz, 1H), 1.45 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, CDCl3) δc: 168.3, 159.8, 152.3, 136.5, 128.8, 126.3, 125.1, 121.9, 119.2, 119.1, 118.0, 114.1, 114.1, 110.6, 109.8, 102.5, 55.6, 41.0, 36.7, 32.0, 15.4. Molecular formula: C_{20}H_{19}NO_{3}. ESI MS (m/z):= 322 (M+H). Analysis calculated for C_{20}H_{19}NO_{3}: C 74.75, H 5.96, N 4.36. Found C 74.78, H 5.92, N 4.33.

4-(1-benzyl-1H-indol-3-yl)chroman-2-one (n)

Physical state: oily. 1H NMR (300 MHz, CDCl3) δH: 7.48 (d, J = 7.7 Hz, 1H), 7.26-7.19 (m, 6H), 7.16 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 5.2 Hz, 1H), 7.09 (d, J = 3.3 Hz, 1H), 7.05 (t, J = 5.19 Hz, 3H), 6.78 (s, 1H), 5.21 (s, 2H), 4.43 (t, J = 6.1 Hz, 1H), 3.72 (dd, J = 7.9, 15.8 Hz, 1H), 3.05 (dd, J = 5.5, 15.8 Hz, 1H). 13C NMR (75 MHz, CDCl3) δc: 168.2, 151.7, 137.2, 137.1, 128.7, 128.6, 128.3, 128.2, 127.7, 126.5, 126.4, 126.1, 124.6, 119.7, 119.2, 117.0, 114.2, 110.4, 50.1, 36.4, 32.6. Molecular formula C_{24}H_{19}NO_{2}. ESI MS (m/z):= 354 (M+H). Analysis calculated for C_{24}H_{19}NO_{2}: C 81.56, H 5.42, N 3.96. Found: C 81.59, H 5.40, N 3.98.

4-(2-phenyl-1H-indol-3-yl)chroman-2-one (o)

Physical state: White solid, mp: >250 °C. 1H NMR (300 MHz, CDCl3) δH: 8.30 (s, 1H), 7.48 (d, J = 6.4 Hz, 5H), 7.32-7.22 (m, 3H), 7.16 (t, J = 8.9 Hz, 2H), 7.37 (d, J = 2.9 Hz, 3H), 4.84 (dd, J = 4.6, 14.1 Hz, 1H), 3.41 (t, J = 15.9 Hz, 1H). 13C NMR (75 MHz, CDCl3) δc: 167.8, 151.3, 137.0, 136.6, 132.2, 128.8, 128.5, 128.0, 127.6, 126.2, 125.8, 124.2, 121.5, 119.9, 118.8, 116.4, 111.7, 108.4, 31.4. Molecular formula: C_{23}H_{17}NO_{2}. ESI MS (m/z):= 340 (M+H). Analysis calculated for C_{23}H_{17}NO_{2}: C 81.40, H 5.42, N 4.13. Found: C 81.41, H 5.09, N 4.16.

4-(6-ethyl-1H-indol-3-yl)chroman-2-one (p)

Physical state: oily. 1H NMR (300 MHz, CDCl3) δH: 8.27 (s, 1H), 7.42-7.34 (m, 2H), 7.18 (s, 1H), 7.16-7.10 (m, 4H), 6.81 (s, 1H), 4.68 (t, J = 6.2 Hz, 1H), 3.30 (dd, J = 7.6 Hz, 15.8 Hz, 1H), 3.12 (dd, J = 11.2, 15.8 Hz, 1H), 2.92-2.84 (m, 2H), 1.39 (t, J = 7.5 Hz, 3H). 13C NMR (50 MHz, CDCl3) δc: 168.6, 151.6, 135.7, 128.6, 128.3, 127.3, 126.2, 125.5, 124.7, 122.1, 121.1, 120.2, 117.0, 116.6, 115.4, 36.4, 32.8, 24.0, 13.8. Chemical Formula: C_{19}H_{17}NO_{2}. ESI MS (m/z):= 292 (M+H). Analysis calculated for C_{19}H_{17}NO_{2}: C 78.33, H 5.88, N 4.81. Found: C 78.35, H 5.85, N 4.80.
Spectral data for synthesized compounds (a-p).